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10/805,973	03/22/2004	Chengyan Zhao	038867/271254	1245

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EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/805,973	ZHAO ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,14-24 and 29-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *20 and 24* is/are allowed.

6)☒ Claim(s) *1-9, 14-19, 23, and 29-31* is/are rejected.

7)☒ Claim(s) *21 and 22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9, 14-24 and 29-31 are pending.

Claims 10-13, 25-28, and 32-41 are cancelled.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/11/2007 has been entered.

This Office Action is in reply to Applicants' correspondence of 1/11/2007. Claim(s) 10-13, 25-28, and 32-41 is/are cancelled; no claims are withdrawn; no claims have been newly added; claim(s) 1, 6, 9, 15, 20, 24 and 30 has/have been amended.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is **NON-FINAL**.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 103 as obvious in view of the teachings of DelRio-LaFreniere et al (2001) and other references. Applicants argue (page 14 of Remarks of 1/11/2007) that the claims require an allele

specific primer which hybridizes to the mutant allele of the wheat AHAS gene (which possesses an A:T base pair at position 1594 of SEQ ID NO: 26) wherein the mutant-allele specific primer comprises a C at the 3'-terminal nucleotide position (whereas conventional hybridization would utilize an A at the 3'-terminal nucleotide position), where providing such a mutant-allele specific primer unexpectedly provides better specificity in that the primer amplifies the mutant allele despite the 3'-teminal mismatch, but does not amplify the wild-type allele. Applicants further argue that DelRio-LaFreniere et al (2001) teaches enhanced specificity of allele specific primers with intentional mismatches at the penultimate and anti-penultimate positions (Remarks p.15), but does not teach enhanced specificity of particular mismatches at the 3'-terminal position. These arguments are persuasive. New grounds of rejection are set forth in this Office Action wherein the teachings of Liu et al (1997) supply the general methodology of a nested allele specific amplification, and the teachings of Kwok et al (1990) supply specific teachings of using a primer with a 3'-terminal C nucleotide for the amplification of a T-containing template but not a C-containing template.

Objection to the Specification

The disclosure is objected to because of the following informalities:

Page 34 line 3 of the specification recites 'first-round PCT' where likely 'first-round **PCR**' is intended.

Appropriate correction is required.

Claim Objections

Claims 1, 15 and 30 are objected to because of the following informalities:

The claims recite the phrase 'G-to-A point mutation that gives to the S653(At)N' where likely 'G-to-A point mutation that gives **rise** to the S653(At)N' is intended.

Appropriate correction is required.

Claim Rejections - 35 USC § 112 2nd¶ - Indefiniteness

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, and 14 are unclear because while the preambles of independent claims 1, 6, and 9 recites 'method for detecting a mutant allele', there is no step in which any mutant allele is in fact detected. The claims may be made more clear if step (c) is amended to define a step of allele detection, as provided in the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 8, 14, 15, 23, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hucl et al (2003) (WO 03/014357) in view of Liu et al (1997) and Kwok et al (1990).

Hucl et al teaches the molecular basis of imidazolinone resistance in wheat plants. Regarding claim 1, the reference teaches that resistance to imidazolinone can be conferred by a guanine to adenine substitution in the AHASL1 gene (referred to in Hucl et al as Asl1), which results in a serine to asparagine substitution (p.7 lns. 1-15; Figure 8 page 17/42; p.13 lns 2-3; Figure 13). Hucl teaches the nucleic acid and deduced amino acid sequences of the AHSAL1 genes of several imidazolinone resistant wheat plants (Fig 8) including the mutation responsible for herbicide resistance. The reference teaches that imidazolinone resistant mutant alleles can be detected by amplifying AHASL1 genes and comparing the amplified gene sequence to that of a known wild-type control (p.17 ln.33-p.18 ln.13; p.20 ln.26-p.21 ln.2). Relevant to step (a) of claim 1, the reference teaches the use of genomic DNA (p.18 ln.11). Relevant to step (b) of claim 1, Hucl et al teaches the portion of the AHASL1 nucleic acid sequence that is responsible for the imidazolinone resistance-mutation, including nucleotides 3-23 of SEQ ID NO: 12 of the instant application (for example see Fig 8, p17/42 of the figures, (SEQ ID NO: 15) the nucleotides encoding the amino acid sequence HVLPMIP(N/S) beginning at amino acid 620).

Regarding claim 8, Hucl teaches that there are AHAS genes on genomes A, B, and D of the *Triticum* wheat plant (p.9 lns. 25-33), and teaches the sequence of the *Imi1*

wheat gene (Fig 8; p.7 lns.1-15), which is the AHASL1D gene on the D genome, as evidenced by Pozniak et al (2004) (p.1439 – Chromosome location of AHAS genes).

Regarding claims 15 and 23, the teachings of Hucl et al are applied to steps (a), (b), and (d) of claim 15 as they were applied to claims 1 and 8 earlier in this rejection. Additionally, Relevant to step (c) of claim 15, Hucl et al teaches the wild-type AHASL1 nucleic acid sequence that is responsible for imidazolinone sensitivity, including the sequence relevant to SEQ ID NO: 10 of the instant application (for example see Fig 8, p17/42 of the figures, (SEQ ID NO: 21) nucleotides that encode amino acids 621-633, HVLPMIPSGGAFKD).

Regarding claim 23, Hucl teaches that there are AHAS genes on genomes A, B, and D of the *Triticum* wheat plant (p.9 lns. 25-33), and teaches the sequence of the *Imi1* wheat gene (Fig 8; p.7 lns.1-15), which is the AHASL1D gene on the D genome, as evidenced by Pozniak et al (2004) (p.1439 – Chromosome location of AHAS genes).

Hucl does not teach the analysis of AHASL1 genes via allele specific PCR using oligonucleotide primers, or primers with mismatches as are required for primers directed to nucleotides 3 to 23 of SEQ ID NO: 12 wherein the 3'-end nucleotide is cytidine (step (b) of claims 1 and 15).

Liu et al teaches a method for the detection of single nucleotide polymorphisms using allele-specific primers (p.390 – Principle of Bi-PASA). Relevant to step (b) of claim 1, the reference teaches a PCR reaction comprised of genomic DNA as a template (p.397 - Methods), dNTPs, a polymerase, forward and reverse gene specific primers (referred to in the reference as primers P and Q), and a mutant-allele-specific

primer (referred to in the reference as primer A) (Figure 1). The reference teaches examples in which the mutant and wild-type allele specific primers are designed to flank the polymorphic position (Fig 1; Table 1). Relevant to step (c) of claim 1, Liu et al teaches the detection of PCR products using gel electrophoresis and ethidium bromide staining (p.397 - Methods). Liu et al teaches that an allele specific primer is capable of annealing to a region of the analyzed gene that is nested between the annealing sites of the gene-specific primers (Fig. 1).

Regarding claims 14 and 29, Liu et al teaches the detection of PCR products using gel electrophoresis and ethidium bromide staining (p.397 - Methods).

Relevant to step (c) of claim 15, Liu et al also teaches the use of wild-type allele-specific-primers for detection of wild-type alleles (Fig 1; Table 1).

Neither Hucl nor Liu teach the use of an allele specific primer with a 3'-terminal cytidine where said primer is used to detect an A nucleotide allele by specifically hybridizing to a T in the template nucleotide.

Kwok provides general teachings concerning the use of different 3'-terminal nucleotides in the amplification of template bases. Kwok et al particularly teaches (p.1001, Table III) the refractory nature of a 3'-terminal C in the amplification of a C-containing template, but the ability of a primer containing a 3'-terminal C in the amplification of a T-containing template.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the mutation detection methods of Hucl et al so as to have used allele-specific and gene-specific primers as taught by Liu et al

and have used a primer with a 3'-terminal C for the specific amplification of the mutant allele. One would have been motivated to use the methods of Liu et al based on the teaching of Liu et al that a nested allele-specific amplification method provides an internal positive control (p.391, right col., lns.6-8). One would have been motivated to use a mutant-allele specific primer with a 3'-terminal C for the detection of the mutant allele based on the teachings of Kwok et al that such a primer will amplify a T nucleotide template but not a C nucleotide template and the teachings of Hucl et al that an herbicide resistance in wheat is based on a G-to-A (thus a template C-to-T) substitution mutation.

Claims 2, 4, 5, 16, 18, 19, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hucl et al (2003) (WO 03/014357) in view of Liu et al (1997) and Kwok et al(1990), and further in view of Stanton (2002) US Patent 6,475,736.

The teachings of Hucl et al in view of Liu et al and Kwok et al are applied to claims 2, 4, 5, 16, 18, 19, and 30 as they were previously applied to claims 1, 8, 14, 15, 23, and 29 earlier in this office action.

Hucl et al in view of Liu et al and Kwok et al teaches a method for the detection of mutant AHASL alleles that confer tolerance to imidazolinone on a wheat plant, including the use of a mutant-allele-specific primer with a 3'-terminal cytidine.

Hucl et al in view of Liu et al and Kwok et al does not teach a pre-amplification step using primers that amplify a product that contains nested annealing sites for the gene-specific primers used to detect specific mutations.

Stanton teaches methods for the analysis of DNA using amplification of polymorphic sites. Relevant to claims 2, 16, and 30 step (b), Stanton teaches that the PCR amplification step of a genotyping procedure can be modified to increase sensitivity by using nested PCR (two rounds of PCR, first with an outside set of primers, then with an inside set) (col.34 lns.35-39).

Regarding claims 4 and 18, Hucl teaches that there are AHAS genes on genomes A, B, and D of the *Triticum* wheat plant (p.9 lns. 25-33), and provides an alignment of the three different imidazolinone resistance genes (Fig. 12). The sequences taught by Hucl et al include primer binding sites for which it would be a necessary property that oligonucleotide primers directed to those regions would anneal to AHASL1A, AHASL1B, and AHASL1D.

Regarding claims 5 and 19, which depend from claims 2 and 16 respectively, Hucl teaches the AHASL1 sequence that includes the sequence relevant to SEQ ID NO: 1 of the instant application (for example see Fig 12, p39/42 of the figures, nucleotides 901-920).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the mutation detection methods of Hucl et al in view of Liu et al and Kwok et al so as to have incorporated a pre-amplification step as taught by Stanton. One would have been motivated to do so based on the teachings of Stanton that a pre-amplification step can increase the sensitivity of the methods (col 34 lns.36-37). One would have had a reasonable expectation of success because Stanton teaches the pre-amplification step in association with PCR based

methods, and the allele detection methods Liu et al are PCR based. Further regarding claims 5 and 19, it would be obvious to use primers comprising the claimed sequence (SEQ ID NO: 1) given the alignment of the three imidazolinone resistance genes (Fig. 12 of Hucl et al) and the consensus sequence that indicates this region is conserved among the three genes, as use of such a primer would allow for subsequent analysis of any of the three AHASL1 genes from any of the three wheat genomes.

Claims 3, 17, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hucl et al (2003) (WO 03/014357) in view of Liu et al (1997), Kwok et al (1990) and Stanton (2002) US Patent 6,475,736 and further in view of Werle et al (1994).

The teachings of Hucl et al in view of Liu et al, Kwok et al and Stanton are applied to claims 3, 17, and 31 as they were previously applied to claims 2, 4, 5, 16, 18, 19, and 30 earlier in this office action.

Hucl et al in view of Liu et al, Kwok et al and Stanton teaches a method for the detection of mutant AHASL alleles that confer tolerance to imidazolinone on a wheat plant. The method utilizes a pre-amplification step, followed by the use of allele-specific primers with intentional mismatches for amplification, and uses mutant and wild-type specific primers.

Hucl et al in view of Liu et al, Kwok et al and Stanton does not teach the use of an exonuclease following the pre-amplification step.

Werle et al teaches the use of exonuclease I to degrade excess primers and nucleotides from PCR products prior to analysis by sequencing. Relevant to claims 3,

17, and 31, Werle et al teaches pre-amplification of a PCR product from genomic DNA, followed by treatment with exonuclease, then analysis of the exonuclease treated PCR product using the same conditions as for PCR of genomic DNA (p.4354, lns.20-36).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the mutation detection methods of Hucl et al in view of Liu et al, Kwok et al and Stanton so as to have incorporated an exonuclease digestion step as taught by Werle et al. One would have been motivated to do so based on the teachings of Werle et al that exonuclease digestion removes factors that interfere with analyses that utilize PCR based methods (p.4354 ln.13-16; p.4354 ln.34-37), and that the exonuclease method is simple to use with minimum sample handling, risk of cross-contamination and amount of DNA template required, and the method is reliable, convenient, and cost effective (p.4355 lns.1-6). One would have had a reasonable expectation of success because Werle asserts that the method has broad applicability in mutational analysis by a PCR based method (p.4355 lns.6-8), and the allele-specific amplification method Liu et al is a PCR based method.

Conclusion and Claim Objections

No rejections under 35 USC 102 or 35 USC 103 are made against claims 6, 7, 9, 20-22, or 24. The novelty of claims requiring SEQ ID NO: 2 (i.e. clams 6 and 20) and SEQ ID NO: 7 (i.e. claims 9 and 24) has been addressed previously in the Office Actions of 03/16/2006 and 09/11/2006. Regarding claims that require SEQ ID NO: 3 (claims 7 and 21) or SEQ ID NO: 4 (claim 22), it is noted that these allele specific

primers contain an intentional mismatch at the –4 position (i.e. each primer contains a G three nucleotides from the 3'-terminal nucleotide, where the G is in a G:G mismatch with the template DNA). There is no motivation in the prior art to specifically create allele-specific oligonucleotide primers in which the –4 position has a G:G mismatch with the template DNA.

Claims 20 and 24 are allowed.

Claims 21 and 22 are objected to as being dependent upon a rejected base claim, but would be allowable if re-written in independent form including all of the limitations of the base claim, including correction of the base claim (claim 15) to remove the Objection to that base claim, and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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